REMARKS

Claims 17-20 remain in the application. Only claim 17 is in independent form. Claims 17-20 have been amended without prejudice in order to expedite the allowance of the present application.

Referring to the Office Action, claims 17-20 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The Office Action holds that the specification is enabling for a marker comprising the OPRM1 +118A allele wherein the marker is indicative of risk for developing alcohol dependency. However, the Office Action holds that the specification does not reasonably provide enablement for markers comprising the OPRM1 +118A allele wherein the marker is indicative of developing substance dependency, wherein the substance is cocaine, marijuana, or substance dependency in its entirety. Moreover, the Office Action holds that one cannot readily anticipate a correlation between the OPRM1 +118A polymorphism and the risk of developing substance dependency, wherein the substance is cocaine, marijuana, or broadly, any substance dependency, because there is insufficient evidence provided in the specification to establish that the findings obtained with alcohol dependency can be extrapolated to all types of substance dependency. Further, in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed (see, page 6, paragraph 1 of the Office Action).

In response thereto, Applicants argue that there is a correlation among substance dependency disorders, such that a risk of one type of dependency is indicative of risks of the other types of dependency. Numerous sources in epidemiologic and genetic literatures provide evidence that there is a substantial link among all of the substance dependent disorders, wherein the substances include, but are not limited to, alcohol, nicotine, cocaine, marijuana, and opiates. For example, data from the National

Comorbidity Study, as set forth in Kessler, et al., proves that an individual with the diagnosis of alcoholism is at an increased risk for all other forms of drug dependencies (e.g., cocaine dependency) by a factor of 9.8 for men and 5.8 for women. Moreover, a study of the Vietnam Era Twin Registry, as set forth in Tsuang, et al., proves that abuse of any drug is associated with use of other drugs. For instance, the within-individual probability of abuse of another drug for marijuana abusers ranges from 0.46 for heroin opiates to 0.80 for psychedelics. Hence, from an epidemiologic perspective, substantial data proves a significant pattern of association among dependencies for a range of legal and illegal drugs.

The above-mentioned epidemiologic studies are further supported by genetic studies of families and twins. A recent study set forth in Merikangas, et al., proves that predominant use of a single drug (alcohol, opiate, cocaine, and/or marijuana) in a proband (diagnosed family member) is associated with increased predominant use in other family members not only of the proband drug, but also of other drugs. This effect holds true even when controlling for the presence of antisocial personality disorders and the use of alcohol. Another study examined drug use among relatives of proband alcoholics (Beirut, et al., 1998). According to this study, approximately fifty percent of brothers and twenty-five percent of sisters carried a lifetime diagnosis of alcohol dependence. Siblings of alcoholic probands, however, were also at substantially increased risk for marijuana dependence, cocaine dependence, and heavy smoking, even after controlling for alcohol dependence in the siblings.

As for various twin studies, it has been demonstrated that large genetic components to risk for disorders, such as alcohol dependence (Heath, 1995) and cigarette smoking (True, et al., 1997) exist. Additionally, it has been shown that a substantial portion of the genetic risk for substance dependence disorders is commonly shared. For example, Beirut, et al., 1998, sets forth evidence for a shared or common vulnerability factor, influenced by genetic and environmental factors, that underlie abuse of a variety of illicit drugs, including marijuana, stimulants, and heroin. The study set forth in True, et al., 1999, which also employed the Vietnam Era Twin Registry, reports that

25.5% of the genetic risk for DSM-IIIR diagnosed alcohol and nicotine dependencies was common to both disorders. This linkage proves that regardless of a choice of drug, substance dependency is a diagnostic entity, and the ability to predict dependence on one type of drug allows for the prediction of dependence on other types of drugs.

As set forth in the specification, the examples show that the frequencies of the risk allele and the risk genotype increase when examining groups identified by dependence on the single drug alcohol (ETOH group) dependency on two drugs (alcohol and nicotine (i.e., ETOH + NIC group)), and multiple drugs (e.g., cocaine, marijuana in addition to alcohol and nicotine (i.e., ETOH + NIC + drug group)). In the examples, the critical research issue is that increasing drug use, regardless of the type, is associated with increasing frequencies of the risk allele and genotype. Hence, in view of what is well known in the art and the examples of the present application, the specification is enabling for markers comprising the OPRM1 +118A allele, wherein the marker is indicative of developing substance dependency. In other words, the specification enables any person skilled in the art to use the invention commensurate in scope with the presently pending claims. Moreover, undue experimentation would not be required to practice the invention as it is claimed in the present application. Reconsideration of the rejection is respectfully requested.

Claims 17-20 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. According to the Office Action, claims 17-20 are indefinite and vague over the recitation of the word "marker" because the claims do not set forth the identity of the polynucleotide "marker." Hence, the Office Action holds that it is unclear whether the "marker" as stated in the claims represents the allele as a whole, a smaller fragment thereof, or a larger fragment of the OPRM1 gene containing the +118A allele.

In response thereto, Applicants have amended the claims to recite the marker as being a "whole allele marker." As a result of the amendment, reconsideration of the rejection is respectfully requested.

Claims 17-20 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Bond, et al. article. According to the Office Action, the Bond, et al. article teaches that isolated nucleic acids comprising the "A" at nucleotide position +118 of the coding region of the OPRM1 gene and the polymorphism, "may have implications for normal physiology, therapeutics, and vulnerability to develop or protect from diverse diseases including the addictive diseases." (See, page 9608 of the Bond, et al., article).

In response thereto, the presently claimed invention is not anticipated by the Bond, et al. article. According to Table 2 of the Bond, et al. article, there is not a statistically significant difference between opioid-dependent cases and control cases in the frequency of the OPRM1 +118A genotypes. Table 2 presents the results of the case association research conducted to determine whether there is a genetic relationship. Specifically referring to the results presented in Table 2, the Bond, et al. article discloses, "there was no significant difference in allele frequencies between opioid-dependent and non-dependent study subjects with all ethnic groups combined. Similarly, no association between this allele and alcoholism or drug abuse of unspecified type was found in the study reported by Bergen, et al." (See, page 9611, column 2, first full paragraph) (emphasis added). Clearly, the Bond, et al. article discloses that there is a failure to demonstrate a relationship between OPRM1 +118A and any form of substance dependency. Additionally, the Bond, et al. article notes that the obtained negative results were consistent with the negative results reported previously by Bergen, et al., 1997.

The Bond, et al. article also describes biochemical, not genetic association, research that illustrates differences in β-endorphin binding affinity between common mu opioid receptors and the A118G variant. The Bond, et al. article does not address differences of any type between control cases and any substance dependence group. Nevertheless, the Bond, et al. article concludes, "for example, response to stress,

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Respectfully submitted,

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Angel Webb

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

17. (Amended) A whole allele marker for determining the risk of developing substance dependency comprising the OPRM1 +118A allele indicating the risk for developing substance dependency.

18. (Amended) The whole allele marker of claim 17, wherein the substance is alcohol.

19. (Amended) The whole allele marker of claim 17, wherein the substance is cocaine.

20. (Amended) The whole allele marker of claim 17, wherein the substance is marijuana.